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*December 16, 2004*

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APPLICATION NUMBER: 60/519,082  
FILING DATE: *November 10, 2003*  
RELATED PCT APPLICATION NUMBER: PCT/US04/37456

Certified by



Jon W Dudas

Acting Under Secretary of Commerce  
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17235 U.S. PTO

PTO/SB/16 (08-03)

Approved for use through 07/31/2006, OMB 0651-0032

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**PROVISIONAL APPLICATION FOR PATENT COVER SHEET**

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 304 054 152 US

INVENTOR(S)					
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Todor N.		Mazgalev		Cleveland, OH	
Additional inventors are being named on the <u>2nd</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
METHOD TO CONTROL VENTRICULAR RATE IN ATRIAL FIBRILLATION PATIENTS					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input checked="" type="checkbox"/> Customer Number:		<div style="border: 1px solid black; padding: 5px; width: 200px; margin: 0 auto;">026418</div>			
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification Number of Pages <u>2</u>		<input type="checkbox"/> CD(s), Number _____			
<input type="checkbox"/> Drawing(s) Number of Sheets _____		<input type="checkbox"/> Other (specify) _____			
<input type="checkbox"/> Application Date Sheet. See 37 CFR 1.76					
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.				<div style="border: 1px solid black; padding: 10px; text-align: center;"> FILING FEE Amount (\$)  80.00 </div>	
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/> No.					
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: _____					

22581 U.S. PTO  
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[Page 1 of 2]

Respectfully submitted,

Date November 10, 2003

SIGNATURE

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(if appropriate)

Docket Number: 501110-20001

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This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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**PROVISIONAL APPLICATION COVER SHEET****Additional Page**

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**Docket Number** 501110-20001

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**[Page 2 of 2]**

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## **Method to Control Ventricular Rate in Atrial Fibrillation Patients**

### **ABSTRACT**

A method is disclosed to control (slow) the ventricular rate for treating patients suffering from atrial fibrillation. The patients' atrioventricular nodal area is injected with autologous fibroblast cells that will grow and create barrier to slow the electrical conduction from the fibrillating atria to the ventricles, thus slowing the ventricular rate during ongoing atrial fibrillation.

### **BACKGROUND OF THE INVENTION**

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia, with an estimated 2.3 million Americans having AF. The prevalence of AF increases with age, from 0.1% among adults younger than 55 years to about 9% of those over 80 years of age. Due to aging population, the number of AF patients is estimated to increase 2.5 times during the next 50 years.

AF is characterized by a rapid and irregular activation of the atria, typically at 400 to 600 pulses per minute in humans. During AF the ventricular rate is no longer under the physiological control of the sinus node. Instead, it is determined by interactions between the rapid atrial firings and the filtering function of the atrioventricular node (AV node). Despite the life saving role of the AV node, without medication AF still results in excessively rapid, irregular ventricular rate. This condition itself can cause severe symptoms, such as palpitation, light-headedness and syncope. Even worse, long-term tachycardia resulting from the uncontrolled ventricular rate could lead to tachycardia-induced cardiomyopathy. A proper rate or rhythm control becomes essential to avoid development of severe heart failure.

Currently there are 2 broad strategic treatment options for atrial fibrillation: rhythm control and rate control. For rhythm control, the treatment is directed toward restoring and maintaining the sinus rhythm. Although ideal, sinus rate cannot be restored and maintained in many AF patients. The other alternative is rate control, the intention is to slow ventricular rate while allowing AF to continue. Recent clinical trials have demonstrated that rate control is as good as rhythm control in terms of morbidity and mortality in the studied AF patients. Thus, rate control and anticoagulation therapy can be the primary therapy in a majority of AF patients.

The rate control strategy during AF essentially deals with efforts to utilize and adjust the filtering properties of the AV node, since the AV node is the only normal structure responsible for the conduction of atrial impulses to the ventricles. Currently drugs (such as digitalis,  $\beta$ -blockers and calcium antagonists) are the most commonly used therapy. However, drugs are not effective in some patients and are not well tolerated by others due to side effects. In those drug-refractory patients, AV node modification and AV node ablation with pacemaker implantation are used currently to alleviate symptoms. However, AV node modification, due to its limited success rate, high recurrence, and higher probability of complete AV block, is recommended only when AV node ablation with pacemaker implantation is intended. Currently AV node ablation with pacemaker implantation is the last choice for

patients with drug-resistant AF. This strategy destroys the AV node and results in lifetime pacemaker-dependency.

It would be ideal to enhance the filtering role of the AV node but not to fully destroy the AV nodal conduction. This is the purpose of the proposed invention with injection of fibroblast cells into the AV nodal area. It's known that fibrous tissue serves as natural isolator within the cardiac conduction system. It has been demonstrated that the AV nodal cells are intermingled with fibrous tissue, which is believed responsible, at least in part, for the normal AV delay. We hypothesized that if fibroblast cells could be injected to this discrete area, they would create further delay of AV conduction, thus, slow the ventricular rate during AF, while avoiding complete AV block.

### **SUMMARY OF THE INVENTION**

The present invention is directed to reducing the ventricular rate in patients suffering from AF as a novel therapeutic approach.

According to the present invention, cultured autologous fibroblast cells are injected to the AV nodal area, either through catheter-based approach or by direct injection through epicardial approach. The delivered fibroblast cells will grow within the AV nodal area, thus, forming more fibrous tissue and creating further delay for the AV conduction. This would result in slowing of ventricular rate in AF patients.

# Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/037456

International filing date: 10 November 2004 (10.11.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US  
Number: 60/519,082  
Filing date: 10 November 2003 (10.11.2003)

Date of receipt at the International Bureau: 23 December 2004 (23.12.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse